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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

009631

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

JUL 27 1992

MEMORANDUM:

Subject: EPA ID # 010182-GEA. Pirimiphos-methyl (Technical): Review of Acute Inhalation Study.

EPA Submission No. S420759
P. C. #: 108102
Tox. Chem. #: 334B
HED Project No. D180069

From: Guruva B. Reddy, D.V.M., Ph. D.
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Toxicology Branch I
Health Effects Division (H7509C)

To: Dennis Edwards Jr./Rita Kumar
Project Manager 19
Registration Division (H7505C)

Thru: Marion P. Copley, D.V.M., D.A.B.T.
Section Head
Section 4, Toxicology Branch I
Health Effects Division (H7509C)

1. **CONCLUSIONS:**

This acute inhalation study (#CTL/P/2795, MRID 415563-04) satisfies the guideline requirements for a study on technical pirimiphos-methyl.

Core - Acceptable
Tox. Category: III

A copy of the DER is attached.

2. Action Requested:

The Compliance Services International on behalf of ICI Americas Inc., has submitted a Acute Inhalation Study (Series 83-1) with pirimiphos-methyl technical in partial fulfillments of the data requirements for registration. The study was reviewed and a copy of the DER is attached.

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3. **Study reviewed:**

Study/Classification	TB-I Comments
83-1 Acute Inhalation Study in Rats ICI Central Tox. Lab., UK Study #: CTL/P/2795 January 9, 1990 MRID #: 415563-04 core - Acceptable Tox. Cat.: III 009631	**Limit Dose** (5.04 mg/L) was tested in Albino rats by Nose-only administration. Acute Inhalation LC_{50} was > 5.04 mg/L (analyzed concentration 4.7 mg/L). Clinical signs included lacrimation, salivation, central nervous system signs (reduced rate and amplitude of breathing, reduced activity, and auditory hypoaesthesia) and inhibition of cholinesterase activity in plasma and erythrocytes on day 2 and in erythrocytes on day 15. The MMAD of the aerosol particles was 1.55 μm and a GSD of 1.49. The % of particle sizes <1 μm was less than 12 %.

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Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 7/20/92
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion P. Copley 7/20/92

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation/Rat

TOX. CHEM. No.: 334B

P. C. #: 108102

MRID No.: 415563-04

GUIDELINE #: 81-3

TEST MATERIAL: Pirimiphos-methyl

SYNONYMS: O-[2-(Diethylamino)-6-methyl-4-pyrimidinyl]-O,O-dimethylphosphorothioate

STUDY NUMBERS: CTL/P/2795

SPONSOR: ICI Americas Inc.
Wilmington, DE 19897

TESTING FACILITY: ICI Central Toxicology Lab.,
Cheshire SK10 4TJ, UK

TITLE OF REPORT: Pirimiphos Methyl: 4-Hour Acute Inhalation Toxicity Study in the Rat

AUTHORS: R. W. Lewis

REPORT ISSUED: January 9, 1990

CONCLUSIONS: Limit Dose (5.04 mg/L) was tested in Albino rats by Nose-only administration (4 hours)

Acute Inhalation LC_{50} was > 5.04 mg/L (analyzed concentration 4.7 mg/L).

Clinical signs included lacrimation, salivation, central nervous system signs (reduced rate and amplitude of breathing, reduced activity, and auditory hypoaesthesia) and inhibition of cholinesterase activity in plasma and erythrocytes on day 2 and in erythrocytes on day 15.

The MMAD of the aerosol particles was 1.55 μm and a GSD of 1.49. The % of particle sizes <1 μm was less than 12 %.

CLASSIFICATION: Acceptable
TOX. CATEGORY: III

The information presented for this Acute Inhalation Toxicity Study in Rats, satisfies the criteria set forth in Subdivision, F Series 81-3.

A. **MATERIALS:**

1. **Test Compound:** Pirimiphos-methyl (Technical), Description: amber liquid, Purity: 90.6%, Lot #: not given, Supplier: ICI Agrochemicals, Fernhurst, Surrey, UK.

2. **Test Animals:** Species: Albino rat, specific pathogen free, Strain: Wister-derived (Alpk:APfSD), Source: Alderly Park, Cheshire, UK., Age: 7 weeks, Weight: males - 225 to 257 g and females - 200 to 225 g. The rats acclimated for 5 days.

   The preliminary run established the optimal conditions. The main study consisted of control and treated groups of 5 males and 5 females each (Table 1).

3. **Environment:** Temperature - 15 to 24°C, Relative Humidity - 50 ± 15%, Light:Dark = 12:12, Air changes/hour: 20 - 30.

4. **Inhalation Conditions:** Exposure by nose-only for 4-hours. The ICI-designed PERSPEX exposure chamber was used in the study. The chamber volume was 9.2 liters. The test atmosphere was generated by pumping (Gilson peristaltic pump) the preheated (40°C) pirimiphos-methyl through glass concentric-jet atomizer and size-selective Gage cyclone generator at an air flow rate of 20 liter/min to an inlet port on the top and exited from the bottom of the chamber. The chamber temperature ranged from 21.7 to 23.0°C and the relative humidity ranged between 36 to 40% for the control group and 25 to 28% for the test group. The control group was exposed to air at a flow rate of 20 liter/min. Following stabilization of the chamber concentration for at least 30 min. nose-only restraining tubes with animals were inserted into holes in the exposure chamber. **Oxygen level in the chamber was not given.**

B. **METHODS:**

1. **Nominal, Aerosol and Actual Concentrations:**

   The nominal concentration was determined based on the loss of material divided by time (min) and airflow (l/min). The concentration of aerosol in the breathing zone was reported determined at approximately 30 minute intervals during the exposure period by drawing the test atmosphere, at a known

flow rate and time, however, the **conditions of air sampling were not given.** The chamber aerosol samples were drawn through a 25 mm diameter Vinyl Metricel (VM-1) filter housed in a Delrin filter holder and concentration was calculated based on the weight of the aerosol on the filter divided by the time and air flow.

The particle size range in the test atmosphere was determined using a Marple Cascade Impactor (Schaefer Instruments Ltd., Wantage, Oxon, UK) during the study. **The sampling times and flow rates were not specified.** The mass collected at each stage was determined gravimetrically and used to determine the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). Actual test substance concentration in the aerosol particles (VM-1 filters and stages of Cascade Impactor) was extracted and quantitated using gas chromatography.

2. **Clinical Observations:** Animals were observed during the exposure frequently, detailed examination at the end of 4-hour exposure and detailed examination from day 1 to 14 (see Attachment 1).

3. **Body weights** were determined on day-1, prior to exposure on day 1 and on days 2, 3, 8 and 15.

4. **Clinical Chemistries -** Plasma and erythrocyte cholinesterase activities were determined on day 2 and at termination.

5. **Necropsy** - Detailed necropsy were performed on all animals euthanized under halothane anaesthesia. Lungs and liver were weighed and fixed in 10 % neutral buffered formal saline. Any abnormal tissues were also saved.

6. The data were analyzed Statistically using two-tailed Student's t-test.

7. **Quality Assurance -** A signed quality assurance statement is enclosed.

D. **RESULTS AND DISCUSSION:**

Table 1. **Summary of Chamber Concentration and Mortality**

Group	Chamber Concentration (mg/L)			Mortality		
	Theoretical	Mean Aerosol	Mean Test Substance	Males	Females	Total
Air				5	5	0/10
Pirimiphos-methyl	7.37	5.04	4.70	5	5	0/10

No animals died during the study. The mean theoretical (nominal), aerosol and measured concentration (test substance) was 7.37, 5.04 and 4.70 mg/l, respectively (Table 1). The difference between the nominal and analyzed concentrations of test substance in the chamber atmosphere was explained as due to the generating system and adsorption to the chamber walls. The particle size distribution of the test material i.e., MMAD was 1.58 μm and a GSD of 1.49. The particles with sizes less than 1.55 μm constituted about 41 % of the population (Table 2). The % of particle sizes < 1 μm constituted less than 12 % of the population and did not satisfy the guideline requirements. However, the study is considered adequate, since it was conducted at the **Limit Dose** of 5 mg/L and the conditions were optimized to generate finer mist or particles.

Table 2. **Aerodynamic Particle Size Distribution**

Size Range (μm)	% by weight in range	
	Analyzed	Total Particulate
≥9.8	0.0	0.1
9.8-6.0	0.1	0.2
6.0-3.5	3.1	3.2
3.5-1.55	55.0	55.6
1.55-0.93	30.0	29.6
0.93-0.52	11.0	10.5
≤0.52	0.9	0.9

Treated animals lost approximately 2 - 3% of the body weight by day 2 post-exposure, but the body weight gain from day 3 - 15 was comparable to the controls. The reduced body weights in the treated animals was predominantly due to stress and exhaustion rather than compound effects. This is further substantiated by comparable weight gains observed from day 3 to 15.

Clinically, all treated rats exhibited reduced rate and increased amplitude of breathing, reduced activity, salivation and auditory hypoaesthesia which lasted for one day; suggesting CNS effects. In males/females, the plasma and erythrocyte cholinesterase levels were significantly reduced on day 2 by 53.2/73.5 and 28.4/44.4 %, respectively, when compared to the controls (Table 3). By the end of the study, the plasma cholinesterase levels were not significantly lower than the controls whereas the

erythrocyte activity was still (males - 19.8 % and females - 12.3 %) significantly lower than the controls, indicating a slower recovery and turn over of erythrocytes compared to plasma proteins. The authors reported that depression in cholinesterase levels and mild depression of the CNS signs were consistent with the findings in other studies on pirimiphos-methyl. In addition, irritation effects such as lacrimation were seen in treated animals during the first few days. Abnormalities due to restraint and discomfort of exposure, such as hunched backs, piloerection, stains around the nose and wet fur were seen in both the treated and controls animals and were considered not related to treatment.

Table 3. **Cholinesterase Levels** (U/L)

Group	**Males**		**Females**	
	Day 2	Day 15	Day 2	Day 15
Plasma				
Control	579	532	1147	1364
Pirimiphos -methyl	**271****	515	**235****	1166
Erythrocyte				
Control	1970	1924	1952	1798
Pirimiphos -methyl	**1406****	**1544***	**1086****	**1576***

* $P \leq 0.05$
** $P \leq 0.01$

Deficiencies: Chamber oxygen levels and chamber air sampling conditions were not provided. Since there were no deaths and no severe toxicity signs which would mask the compound effects, it is assumed that oxygen levels were normal (20 %). It is also assumed, that standardized conditions were used to sample the chamber atmosphere, due to the fact that chamber concentrations were expressed as mg/L and this unit of measure is the basis for determining the LC_{50}.

CONCLUSIONS:

The toxicity category is III

As presented, the study satisfies the requirements set forth in Subdivision F Guidelines, 81-3 for acute inhalation study.

Attachment 1

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PIRIMIPHOS-METHYL: 4-HOUR ACUTE INHALATION TOXICITY STUDY IN THE RAT

CLINICAL EXAMINATION METHODOLOGY

The check list followed during detailed clinical examination of the animals.

Check	Method
Condition of fur	Look for piloerection, wetness, cleanliness etc.
Respiration	Whether abnormally fast or slow, listen for signs of gasping, wheezing etc.
Motor activity	Whether subdued, staggering, poor limb co-ordination etc.
Skin colour	Look at feet/ears for signs of redness/pallor and increase in visible blood vessels.
Salivation	Look at and around mouth for mucus, wetness etc. Also note colour of saliva.
Faeces	Note presence and degree of diarrhoea.
Righting reflex	Whether animal immediately rights itself when rolled onto its back.
Condition of eyes	Whether inflamed, watering, opaque, bulging etc.
Palpebral reflex	Touch corner of each eye with a fine hair. Animal should blink if normal.
Pinna reflex	Touch each ear with a fine hair. Animal will twitch ears if normal.
Foot withdrawal reflex	Pinch animals foot. Animal will jump if normal.
Response to sound	Make a sharp noise. Animal will jump if normal.
Visual placing	Lift animal by the tail and slowly move downwards towards edge of bench. A normal animal will attempt to seize the edge as soon as it is within reach.
Splay reflex	Lift animal by the tail. A normal animal splays and extends the hindlimbs.

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Chemical:	**Pirimiphos-methyl (ANSI)**
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HED File Code	**13000 Tox Reviews**
Memo Date:	**07/27/1992**
File ID:	**TX009631**
Accession Number:	**412-01-0083**

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